Medication Adherence in Patients with Low Health Literacy

By

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Literature Review Abstract

Objective: To perform a brief review of interventions designed to improve medication adherence in persons with low literacy.

Data Sources: We searched PubMed up to 2010 and Google Scholar from 2000 to 2010. Search strategies were reviewed with a health sciences librarian and the search results supplemented with recommendations from clinical faculty.

Study Selection: We included published clinical trials and systematic reviews that focused on interventions to improve medication adherence or that studied interventions to improve health outcomes in low-literacy participants. One reader reviewed each article for inclusion and verified the selection with clinical faculty.

Data Extraction: One reviewer abstracted data from each study into an evidence table. Two appraisal templates were used to guide the abstracter to grade each article based on potential selection bias, measurement bias, confounding, and analysis. Each study was a grade of good, fair, or poor. Final table details were reviewed by clinical faculty.

Data Synthesis: We identified 10 articles for this review, 7 of which examined interventions designed to improve medication adherence and 3 that examined interventions designed to improve health outcomes in low-literacy participants. The results of the studies were mixed with some showing significant improvement in medication adherence and others showing no effect. For interventions targeting low-literacy participants, mixed results were also seen with some interventions working better for low-literacy persons and others having the same effect for high- and low-literacy study participants. Medication adherence was measured in various ways, making it difficult to compare and draw conclusions about effective intervention strategies. Similarly, the health outcomes measured for interventions targeting low-literacy persons varied and the mixed results made conclusions about the most effective strategies difficult.

Conclusions: Numerous interventions have been developed to try and improve medication adherence and to improve health outcomes for low-literacy populations. The effects of these intervention strategies are mixed and variations in outcome measures and study methodologies make it difficult to draw conclusions about the best strategies. More standardized methods of measuring medication adherence are needed so that interventions studies can be compared and the most effective interventions better identified and understood. Further research is needed to determine the best interventions to improve medication adherence, as well as their effect on measurable health outcomes. Further research is also needed on interventions targeting low-literacy persons, as current strategies have not proven to be consistently effective in this population.

Brief Literature Review of Medication Adherence and Health Literacy Intervention Trials

Introduction

Medication adherence is an important part of individual's health. It is estimated that nonadherence to prescribed medications is responsible for nearly 125,000 deaths per year, and low adherence rates lead to increased ambulatory care visits, ED visits, and hospitalizations.[1, 2] Medication adherence has been defined as how well a person's behavior, including taking medications and following dietary or lifestyle change recommendations, coincides with the medical or health advice he or she has received.[1] Research has consistently shown that average medication adherence is 50% for patients with chronic disease, and patients with low adherence rates are three times less likely to have good health outcomes.[3, 4] The rates and effects of low adherence rates have prompted studies to explore the causes of medication nonadherence, in the hopes that increasing medication adherence will lead to improved health outcomes. Key contributors include the following: adverse effects to treatment, poor instructions, inability to pay for medications, poor relationships between the patient/care-taker and health professional, polypharmacy, lack of understanding about disease management, asymptomatic conditions (such as hypertension), and low literacy.[5, 6] Inadequate medication adherence has been called the most important modifiable aspect of chronic disease management,[4] making it an important target for effective interventions.

In addition to its contribution to low adherence rates, low literacy - described as the inability to read, write, and use numbers effectively - has been associated with numerous adverse health outcomes.[7] Studies have demonstrated the association between lower health literacy levels, less medication knowledge, and lower medication

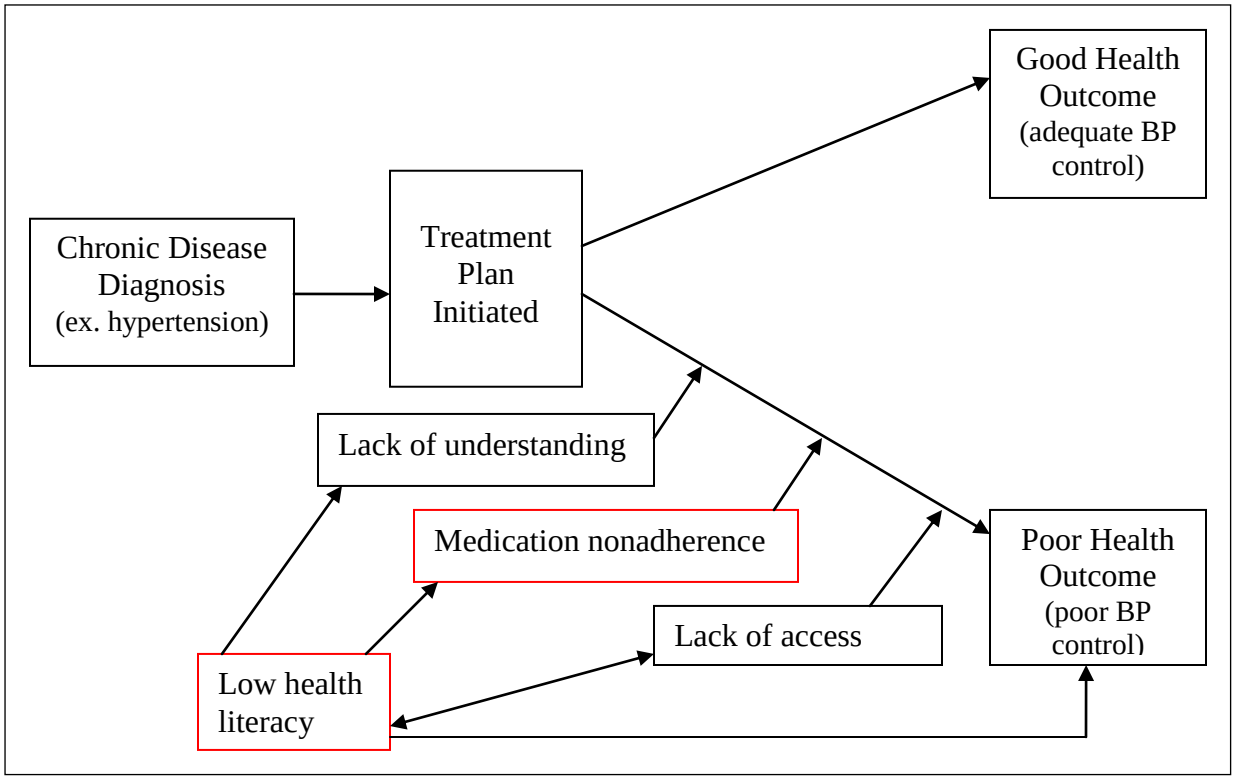
adherence.[3] In the US, more than 1/3 of the residents have low health literacy rendering them unable to determine things like the timing of their medication from common prescription drug labels.[3] The way in which low health literacy leads to poor health outcomes is not completely understood. Pignone et al suggest two causal pathways from low literacy to poor health – direct and indirect (see Figure 1).[7] The direct pathway implies that low literacy may have a direct negative effect on health, potentially for diseases in which complex self-care is needed. The indirect pathway suggests that low literacy is commonly associated with poverty and poor health access, which are known to be associated with poor health. The relationship between medication adherence and health literacy might imply a joint effect on patient's poorer health status and health outcomes, though the association with health outcomes is yet to be established.

In order to attain a greater understanding of the interaction between low health literacy and medication nonadherene, as well as nonadherence's effect on health outcomes, we reviewed current literature on these topics. The aim of this review was to determine what interventions are effective for improving medication adherence in patients with low health literacy.

Methods

We searched the PubMed database for peer-reviewed published articles using the MeSH search terms "medication adherence" and "literacy." From this initial search, 188 articles were found. We then limited the search to clinical trials, English language, and study subjects over 19 years age. This search yielded 30 articles. Fifteen abstracts were reviewed because the title suggested that the article fit the initial selection criteria of an intervention with the primary or secondary outcome of medication adherence. After

Figure 1: Conceptual Model for the Relationship Between Health Literacy and Medication Adherence



review of the abstracts, 6 of the 15 articles were selected because they were actual clinical trials. Those excluded were observational studies looking at associations between some participant characteristic(s) and nonadherence.

We supplemented the PubMed seach with a search of Google Scholar, as suggested by a UNC Health Sciences Library health literature search specialist. We searched Google Scholar using the search terms "medication adherence," "literacy," "interventions," and "clinical trials" (2000 to June 2010) limited to medicine, pharmacy, and veterinary science publications and no patents. 1,630 articles were found and 120 titles were reviewed. Due to time restrictions and many of the last 30-40 titles reviewed not relating much to the topic of interest, all 1,630 titles were not reviewed. 42 abstracts whose titles seemed to fit the initial selection criteria were reviewed, from which 16

articles were selected. Search strategies utilized prior to the implementation of this final strategy are detailed in the Literature Search Outcomes table. The strategy outlined above was chosen because it yielded the best study results for the best defined question, agreed upon by our clinical faculty advisors.

The quality of each article was given a rating of good, fair, or poor using a Critical Appraisal of Health Literature tool designed by faculty of the Health Care & Prevention Program at the UNC Gillings School of Global Public Health for their critical appraisal courses. This tool is designed for the reviewer to assess potential selection bias, measurement bias, confounding, and the adequacy of the analysis to determine the overall internal and external validity of each clinical trial, yielding a final quality grading. A similar tool for systematic reviews and meta-analyses guides the reviewer through an evaluation of the search and appraisal strategies utilized, the presence of a focused question, the authors' dealings with publication bias and heterogeneity, and statistical analysis when applicable to yield a quality grading. Each article was read and rated using these tools by the primary author, with suggestions and corrections from clinical faculty familiar with health literacy and medication adherence literature.

Results

A total of 21 studies were read to determine the best representative sample for the answer to our research question. Studies were excluded if they were conducted outside of the US and if they did not either target low-literacy participants or have medication adherence as a measured outcome. We also did not include studies that were contained in systematic reviews that we selected for review. Some articles did not report final study results and were therefore excluded. Our initial hope was to only include clinical trials

that targeted low-literacy participants and looked at medication adherence as the primary outcome. However this scope proved to be too limited and yielded only 3 studies utilizing our search strategy. We decided to include clinical trials or reviews of clinical studies that either evaluated the effect of an intervention on some health outcome in low-literacy participants or looked at interventions for medication adherence, including 7 of the 21 studies found using our search strategy. Two additional articles were included from the review of citations for the selected articles, and 1 article was included at the recommendation of our clinical faculty. Thus, a total of 10 articles were included in this review.

The studies included were overall of good quality, yielding mixed results for how interventions affect the health of low-literacy individuals and medication adherence rates (see Literature Review Table). Seven of the 10 studies focused on medication adherence as a primary outcome. Three of these studies found that the interventions reviewed or studied were effective and improved medication adherence.[4, 6, 8] Interventions in these studies included standardized medical education, special medication disposal packaging, using icons/pictures on medication instructions and containers, written and verbal instructions, simplifying or modifying dosing regimens, drug and disease education, review of medications, and side effect management. One of these 3 studies was randomized controlled trial and 2 were systematic reviews. Participant demographics for these studies and review varied as did the measures to assess medication adherence. The other four studies focusing on medication adherence included 2 systematic reviews and 2 randomized controlled trials.[1, 3, 5, 9] Neither RCT found that the intervention tested had significant effects on medication adherence. These interventions were a decision-aid tool for diabetes mellitus patients and a low-literacy hospital discharge tool with icons and

pictures to help understanding of heart failure patients' medication regimen.[3, 9] The two systematic reviews found mixed effects of interventions seeking to improve medication adherence, among patients with chronic diseases. Interventions included both behavior and educational approaches to adherence, including pharmacist education, tailored counseling sessions, and mail and telephone reminders to participants. While improvements in medication adherence were seen, the significance of the interventions' impact varied and, for patients with multiple chronic conditions, was weak.[5]

For the three studies focused on interventions targeting low-literacy individuals, the results were mixed. One of these studies was randomized controlled trial,[10] and two were systematic reviews.[7, 11] The RCT focused on low-literacy patients and did not report any significant effect on medication adherence or any other primary outcome. This intervention for adult patients with arthritis included a booklet written at the $5^{th} – 8^{th}$ grade reading level and 2 appointments with a health educator.[10] No difference in medication adherence was seen between the intervention and control groups. Both of the systematic reviews aimed to discuss interventions designed to improve health outcomes for patients with low health literacy. Mixed intervention effects were reported for various low-literacy interventions which included the following: brochures, health education/management interventions, computerized tools, verbal or oral presentations, simplified language, pictorial information, and attempts to improve access to health information. In Pignone et al, some interventions benefited low-literacy patients while others benefited high-literacy patients, and still others had no differential effect.[7] Clement et al found that despite many studies showing beneficial outcomes for the intervention group, most were of mixed statistical significance.[11]

Discussion

Strategies to improve medication adherence, particularly in individuals with low health literacy, are diverse and of varied effectiveness. Overall the interventions discussed in these studies did not demonstrate consistent increases in medication adherence nor consistent significant improvement in health outcomes for low-literacy patients. One of the issues continually discussed by study authors was the need for a better understanding of what effects medication adherence and for a more standard measure of medication adherence.[1] The use of pill counts, self-reports, MEMS caps, and pharmacy refill records all measure adherence differently, and, in combination with varied duration of follow-up post-intervention, make it difficult to compare intervention effects. Poor or inconsistent methodology and participant demographic reporting also make it difficult for conclusions to be drawn about the most effective interventions.[1] There are numerous contributors to medication nonadherence by patients, spanning from cost of medications to lack of understanding to fear of adverse side effects. Low-health literacy modifies medication adherence and health outcomes through various means. The complexity of these two health care challenges make targeted interventions difficult to develop. Combinations of behavioral and educational strategies seem to be best, although how and where and how long interventions are delivered make a difference. Educational interventions are said to be useful in situations with patients who are willing to take their medication but lack information or understanding of how to do so, and for individuals whose misunderstanding of their medication makes them nonadherent.[1] Behavioral interventions conducted without direct educational aims do not always increase medication adherence, but have been effective.[1, 4] Complex or combined interventions are

said to be more effective for low-health literacy patients, but significant health outcomes have yet to be consistently demonstrated.[11]

The best interventions to target low health literacy populations and to improve medication adherence still need to be determined. Patients with low health literacy are less likely to understand the effects of their medications and are more likely to make errors in the dosing and frequency of their medications.[12] Over 800 peer-reviewed studies have demonstrated a mismatch between the literacy skills of most US adults and the skills needed to understand basic health materials.[10] Targeting lower health literacy as a factor in poor medication adherence is an opportunity for the development of interventions.[12] Current interventions benefit patients regardless of literacy level, while others are more effective for either low or high literacy individuals.[11] Future research in this area is important for potentially improving health outcomes, and needed for effective interventions to be developed.

Manuscript Abstract

Background: Numerous studies have examined strategies on how best to help patients improve medication adherence for improved chronic disease care. Poor health literacy can have important effects on patient's understanding of disease and subsequent health outcomes. It is critical to understand how health literacy affects interventions to help improve medication adherence.

Methods: A secondary analysis of a randomized controlled intervention trial conducted at 2 university-affiliated primary care clinics. Primary outcome was self-reported medication adherence at 24 months using a Morisky score. Data was analyzed on 636 adults with hypertension who were followed over 24 months in the Taking Care of Your Blood Pressure (TCYB) study and randomized to one of 4 intervention arms: usual care, home BP monitoring, nurse-tailored behavioral intervention, or a combination of home BP monitoring and nurse-tailored intervention. We evaluated the impact of the intervention on medication adherence using logistic regression and compared treatment effects according to low vs. adequate literacy, as determined by Rapid Estimate of Adult Literacy score (<61 low literacy).

Results: Baseline demographic characteristics for the 636 patients randomized to one of 4 trials arms in the TCYB study varied significantly by literacy status for race ($p<0.001$), education level ($p<0.001$), income ($p<0.001$), hypertension knowledge ($p<0.001$), and self-reported medication nonadherence ($p=0.023$). At 24 months, the proportion of nonadherent patients decreased in usual care and all 3 intervention arms, however the odds of nonadherence for each intervention arm relative to usual care, controlling for baseline adherence, was not significant. Evaluation of the interaction between literacy and the intervention effect showed a trend towards significance. Stratified analysis of medication adherence at 24 months for low and high literacy participants demonstrated that nonadherence decreased in each randomization group. The odds of nonadherence were not significant for any intervention arm relative to usual care, controlling for baseline adherence, for the adequately-literate patients. The odds of nonadherence were significant only for the combined intervention group relative to usual care [OR 3.546, 95% CI 1.01 to 12.48, $p=0.049$].

Conclusions: Self-reported medication adherence improved for each group in the TCYB study. No significant difference was seen between participants' odds of nonadherence by intervention group relative to usual care. These results suggest that patients with low literacy were not more likely to show improve adherence with the intervention and in fact may have been less likely to improve than those with adequate literacy. This effect may be attributable to the surprisingly large decrease in nonadherence for low-literacy usual care participants, but warrants further investigation. Further research is needed to understand the complex relationship between literacy and adherence, and the effect of multi-faceted interventions on adherence.

Manuscript

Introduction

Hypertension is the leading risk factor for cardiovascular disease (CVD), which is responsible for 1 in 3 deaths in Americans.[13] Currently more than 65 million American adults carry the diagnosis of hypertension, and it is estimated that 50.1% have their blood pressure (BP) under control.[13, 14] Improved BP control has been set as one of the national health objectives.[15, 16] Meeting BP control targets in individuals with hypertension requires not only adequate recommendations from the physicians treating patients, but patient understanding of disease, treatment, and adherence to the treatment plan. Barriers at multiple levels – including patient nonadherence – can prevent good BP control, and lead to poor outcomes for hypertension patients.

Treatment nonadherence is a significant problem and has been cited as an important barrier to hypertension management.[17] Suboptimal health outcomes and higher health costs, estimated up to $100 billion annually, result from patients failure to adhere to medication regiments.[17] Patients have reported that lack of understanding about their condition and prescribed medications are important determinants of medication adherence.[18] To improve adherence, interventions must target the individual patient barriers.[19]

Functional health literacy may be one such barrier as it has been shown to have significant effects on patient medication adherence.[18] The American Medical Association defines health literacy as "a constellation of skills, including the ability to perform basic reading and numerical tasks required to function in the health care environment."[20] According to the 2003 National Assessment of Adult Literacy, 22% of US adults have

basic health literacy and 14% have below basic health literacy.[21] Literacy may modify adherence through a patient's lack of understanding of their disease, their medications, or the importance of following a treatment plan. Health literacy is, therefore, a potential target for improving adherence to medication regimens.

Low health literacy is associated with poorer patient compliance in medication adherence and lifestyle improvement, and literature suggests that non-adherence is a significant problem among patients with chronic disorders, such as hypertension.[15, 22] In fact, survival for patients with hypertension is directly related to their completed schooling.[23] Studies that have targeted patients with low health literacy have demonstrated mixed results, with some benefiting more low-literacy than high-literacy patients and others showing no difference in outcomes.[7] Interventions that focus on low literacy affect knowledge and health behavior, which can both improve patient adherence to medications and lifestyle changes,[18, 22] but questions remain about the effect on overall health outcomes.[24]

The purpose of this study is to examine the effect of patient-centered interventions on antihypertensive medication adherence for patients of low and adequately health literacy. The Taking Care of Your Blood Pressure (TCYB) study was a randomized controlled intervention trial that tested 3 patient-centered, self-care and behavioral intervention arms against usual care for patients with hypertension in order to improve BP control. Previous studies have demonstrated that comprehensive management programs, such as that used in the TCYB study, benefit patients of low literacy more than patients with high or adequate literacy.[25] Thus the present study evaluates the interventions by focusing on self-reported medication adherence changes in patients with

adequate and low literacy to determine whether these interventions are an effective strategy for improving adherence in patients with lower health literacy.

Methods

Study Design

The TCYB study was a 2-year randomized intervention trial. There were four trial arms: usual care from primary care providers; home BP monitoring; tailored behavioral intervention delivered by a nurse; and a combined intervention with both home BP monitoring and the nurse-delivered behavior intervention. The primary outcome for the TCYB study was the proportion of patients with controlled blood pressure. Study methods and results have been presented previously and showed the most improvement in the combined intervention group after 24 months.[26] For this analysis, participants from all 4 trial arms were compared to determine the intervention effect on self-reported antihypertensive medication adherence. Improvement in self-reported adherence was compared across all trial arms and stratified by health literacy to determine whether any intervention showed more improvement for low-literacy participants.

Participants

TCYB was conducted in 2 Duke University Health System (DUHS) primary care clinics in Durham, NC, and 636 patients were included. To be eligible for participation individuals had to (1) be enrolled with a primary care physician at the included clinics for at least 12 months prior to study recruitment, (2) have a diagnosis of hypertension for at least 12 months, (3) currently report taking antihypertensive medications, and (4) reside in one of the pre-specified zip codes around DUHS. Potential participants were identified

through weekly data extractions from the DUHS billing and appointment database for the 2 selected primary care clinics – one staffed by 7 internal medicine faculty and the other by 85 internal medicine residents under the supervision of faculty physicians. Recruitment occurred from May 2004 to December 2005. Letters were mailed to 2060 potentially eligible patients from their primary care provider. Letters included information about the study and made the patients aware that a member of the study team might contact them about participation. The study team attempted to contact 1728 individuals by phone, and 656 patients were enrolled and consented. In the recruitment process, 365 could not be reached by letter or phone, 634 individuals declined, 214 were deemed ineligible, and 191 were not consented for other reasons. During the baseline interviews, 20 more patients were excluded. The remaining 636 patients were randomized to one of the four intervention arms. Randomization was done in block using consecutively numbered envelopes with sequences maintained by a study statistician outside of the 2 enrollment clinics. Research assistants were blinded to the number of blocks, and randomization was stratified by enrollment site and by health literacy.

Measures and Outcomes

For the present study, all randomized groups were used to evaluate improvement in self-reported medication adherence from baseline to 24 months (or dropout), stratified by health literacy. Self-reported medication adherence was collected at baseline and at 24 months from participants at follow-up visits during the TCYB study. We collected demographic information on age, gender, race/ethnicity, marital status, support in the home, education, employment, income, smoking status, alcohol intake, understanding of disease, and medication adherence by participant self-report. Individuals reporting that

they only had enough money to pay bills by cutting back on other things, or that they had difficulty paying bills no matter what they did were defined as having inadequate income. BP measurements were obtained during the initial visit and subsequent follow-up visits for all participants. Antihypertensive medication adherence was assessed through 5 questions during the baseline interviews. The questions were as follows: (1) I sometimes forget to take my BP medicine; (2) I am sometimes careless about taking my BP medicine; (3) when I feel better, I sometimes stop taking my BP medicine; (4) if I feel worse when I take the BP medicine, sometimes I stop taking it; and (5) I have skipped doses in the past month. Participants were characterized as nonadherent by their answers according to the Morisky scoring method. The Morisky scoring method is an adherence measure (alpha reliability = 0.61) designed for and tested in patients with HTN.[27] It focuses on barriers to patients taking their medication, and has proved reliable and valid for initial adherence assessment as well as for monitoring adherence over time.[27] Health literacy was measured using the Rapid Estimate of Adult Literacy in Medicine (REALM). Patients with a score of 0-60 (below 9th-grade reading level) were considered low literacy and patients with a score of 61-66 (greater than or equal to 9th-grade reading level) were considered to have adequate literacy. For the purposes of this study, the hypertension knowledge variable was created because understanding of disease has been found to be associated with health literacy. The following questions were used to assess participants' knowledge of hypertension: (1) if someone's blood pressure is 160/100, it is high, low, or normal; (2) once someone has high blood pressure it usually lasts for a few years, 5 to 10 years, or for the rest of their life; (3) losing weight and exercising every day usually makes blood pressure go up, go down, or stay the same; (4) decreasing blood pressure can reduce the risk of kidnesy problems – true or false' (5) African-Americans

are at a higher rate of risk for high blood pressure – true or false; and (6) having diabetes and high blood pressure is not a serious combination – true or false. Each question also had the option don't know as a response. The number of overall correct answers was graphed to evaluate the distribution and a cut-off of 6 correct responses out of the 6 questions was considered adequate disease knowledge.

Intervention

The groups compared in this study were the no intervention/usual care, nurse-conducted behavioral intervention, home BP monitoring, and the combined intervention groups from the TCYB trial. Usual care consisted of regular hypertension treatment from the patient's primary care provider. Participants in the home BP monitoring intervention group received a home BP monitor and were trained in home use by 2 research assistants. Patients were asked to measure their BP 3 times a week on 3 separate days at the same time of day, to record these values in a log, and to mail the log in every 2 months. The tailored behavioral self-management intervention was carried out by 1 nurse making bi-monthly telephone calls to this group of participants. The encounters (telephone conversations) focused on improving adherence to dietary changes, weight loss, reduced sodium intake, regular moderate-intensity physical activity, smoking cessation, and moderation of alcohol intake. A group of modules were implemented during each call, and information was presented at a less than 9th-grade reading level.[28] The combined intervention consisted of both the home BP monitoring and a nurse-directed behavioral self-management intervention.

Statistical Analysis

Demographic information collected during baseline interviews was analyzed to examine descriptive characteristics by literacy level. Student's t-test and chi-square analysis was used to compare the adequate- and low-literacy participants according to age, gender, race/ethnicity, education, employment, income, smoking status, alcohol intake, baseline nonadherence, hypertension knowledge, and baseline BP measurement.

Chi-square analyses were run to evaluate self-reported medication adherence by randomization arm at 24 months and compare to baseline nonadherence. A logistic regression model was used to estimate the odds of nonadherence for each intervention group relative to usual care controlling for baseline adherence. A second logistic regression model adjusting for literacy by intervention, and controlling for baseline adherence, was used to evaluate whether literacy had an impact on the intervention effect. Chi-square analysis was run to compare the proportion of nonadherent participants for both low and adequate literacy at baseline and at 24 months. The odds of nonadherence for each intervention group relative to usual care and stratified by adequate and low literacy were estimated using a logistic regression model, adjusted for baseline adherence.

Results

Results for Demographic Characteristics by Literacy Level

636 patients were enrolled in the TCYB trial, randomized to usual care or 1 of 3 interventions (159 usual care, 158 home BP monitor, 160 nurse-administered behavior intervention, and 159 combined intervention). Descriptive characteristics were very similar for each intervention group (previously reported).[26] Randomization was stratified by enrollment site and literacy, such that the number of low-literacy participants was

nearly equivalent in each trial arm: 43 usual care, 44 home BP monitor, 44 nurse-administered behavior intervention, and 43 combine intervention. Initial exploratory analysis looked at differences in the demographic characteristics of adequate- and low-literacy participants. Participants with low health literacy were significantly more likely to report non-white race, lower educational attainment, inadequate income, lower hypertension knowledge, higher medication nonadherence, and have higher initial systolic and diastolic BP ($p<0.05$ for all comparisons, see Table I).

Table I: Descriptive Characteristics

Characteristic	All Participants (n=636)	Adequate Literacy° (n=461)	Low Literacy° (n=174)	P value
Age (years (SD))	61.2 (12.3)	61.6 (12.2)	60.2 (12.5)	0.195
Male gender	34.0	33.2%	35.6%	0.562
Race White Black Other	 48.4% 49.0% 2.5%	 61.2% 37.3% 1.5%	 14.9% 79.9% 5.2%	 <0.001
Latino/Hispanic Ethnicity	1.1%	1.3%	0.6%	0.538
Education 0-6th grade 7-9th grade 10-12th grade more than high school	 2.8% 5.8% 27.7% 63.5%	 0% 1.1% 21.3% 77.6%	 10.3% 18.4% 44.8% 26.5%	 <0.001
Employment Full or part-time Retired Unemployed	 39.3% 40.4% 20.3%	 45.1% 41.0% 13.9%	 24.1% 38.5% 37.4%	 <0.001
Inadequate income	19.0%	11.3%	39.6%	<0.001
Current smoker	28.2%	26.3%	33.0%	0.188
High alcohol intake*	1.4%	1.5%	1.2%	0.849
Adequate HTN Knowledge^	79.4%	86.9%	58.5%	<0.001
Blood Pressure (mmHg)† Systolic Diastolic	 124.8 71.2	 123.6 70.7	 128.2 72.7	 0.004 0.032
Non-adherent (at start of study)	35.8%	27.8%	56.2%	0.023

°literacy was randomized by trial arm, table shows general comparison for all participants
*high alcohol intake based on individual reporting >14 drinks/wk
^adequate hypertension knowledge defined as participant answering 6/6 questions correctly
†variable created to take the mean of two digital BP measurements taken by research assistants during baseline interview/initial clinic visit

Results for Nonadherence by Intervention Arm

Of the 636 patients enrolled in TCYB, 35.8% were nonadherent at baseline. Over the 24-month study, self-reported medication adherence decreased in each randomization arm: from 32.1% to 25.0% in the usual care group; 35.4% to 25.4% home BP monitor group; 40.6% to 28.4% in the nurse-administered behavior intervention group; and 35.0% to 25.7% for the combined intervention group (see Table II). 150 participants were lost to follow-up during the study secondary to withdrawals (n=33), exclusion (n=26) and death (n=15). We used a logistic model to determine if either intervention had a significant effect on self-reported medication adherence. None of the intervention arms had a significant effect on nonadherence relative to usual care. The odds of nonadherence for each intervention arm relative to usual care, controlling for baseline adherence, were 1.04 [95% CI: 0.54 to 2.00, p=0.911] for home BP monitor, 1.00 [95% CI: 0.53 to 1.88, p=0.996] for nurse-administered intervention, and 1.05 [95% CI: 0.55 to 2.03, p=0.879] for the combined intervention (see Table II).

To determine if there was a difference in how the interventions affected nonadherence for low vs. adequate-literacy participants, we evaluated the interaction between literacy and intervention on the outcome of 24-month adherence. There was a trend towards significance for the interaction between literacy and nurse-administered intervention (p=0.093) and the combined intervention (p-0.023). Because of this trend, we stratified nonadherence by adequate-literacy participants and low-literacy participants (see Tables III and IV). For the adequate literacy participants, the odds of nonadherence were not significant by intervention arm relative to usual care. Nonadherence decreased increased slightly (23.3% to 24.7%) in the usual care group, but decreased in each intervention arm. The home BP monitoring group had a nonadherence odds of 0.897

[95% CI: 0.51 to 1.97, p=0.786], 0.689 for the nurse-administered behavior intervention group [95% CI: 0.32 to 1.47, p=0.326], and 0.646 for the combined intervention group [95% CI: 0.29 to 1.41, p=0.282].

Table II: Unadjusted evaluation of intervention effect on self-reported medication adherence

	Nonadherence T=0 (n=636)	Nonadherence T = 24 mo. (n=486)*	Odds Ratio [95% CI]	P value
Usual care°	32.1% (n=159)	25.0% (n=132)	ref	--
Intervention Arm 1: home BP monitor	35.4% (n=158)	25.4% (n=114)	1.04 [0.54, 2.00]	0.911
Intervention Arm 2: nurse-administered behavior intervention	40.6% (n=160)	28.4% (n=127)	1.00 [0.53, 1.88]	0.996
Intervention Arm 3: combined intervention	35.0% (n=159)	25.7% (n=113)	1.05 [0.55, 2.03]	0.879

*change in number of participants due to loss of follow-up
°usual care is referent group

For the low-literacy participants, nonadherence decreased in each randomization group. The odds of nonadherence at 24 months for each intervention arm relative to usual care were not significant for home BP monitoring or the nurse-administered intervention, but they were for the combined intervention group. The odds of nonadherence for low-literacy participants in the home BP monitor group were 1.49 [95% CI: 0.46 to 4.79, p=0.504], 2.22 for the nurse-administered intervention group [95% CI: 0.73 to 6.78, p=0.161], and 3.546 for the combined intervention group [95% CI: 1.01 to 12.48, p=0.049].

Discussion

In a randomized controlled trial that compared a behavior intervention of home BP monitoring, a nurse-administered tailored self-management intervention, and a combined intervention to improve blood pressure, we evaluated the effect of the interventions on self-

reported antihypertensive medication adherence over 2 years. There was improvement in self-reported medication adherence for the usual care and intervention groups, and there did not seem to be any significant difference in the odds of nonadherence over 2 years between the groups.

Table III: Evaluation of intervention effect on self-reported medication adherence for adequately-literacy participants

Adequate Literacy Participants	Nonadherence T=0 (n=407)	Nonadherence T = 24 mo. (n=359)*	Odds Ratio [95% CI]	P value
Usual care°	23.3% (n=108)	24.7% (n=99)	ref	--
Intervention Arm 1: Home BP monitor	27.2% (n=102)	21.8% (n=85)	0.897 [0.508, 1.971]	0.786
Intervention Arm 2: Nurse-administered behavior intervention	34.5% (n=95)	23.2% (n=91)	0.689 [0.315, 1.468]	0.326
Intervention Arm 3: Combined intervention	26.1% (n=102)	19.6% (n=84)	0.646 [0.292, 1.431]	0.282

*change in number of participants due to loss of follow-up
°usual care is referent group

Table IV: Evaluation of intervention effect on self-reported medication adherence for low-literacy participants

Low Literacy Participants	Nonadherence T=0 (n=227)	Nonadherence T = 24 mo. (n=127)*	Odds Ratio [95% CI]	P value
Usual care°	55.8% (n=51)	25.7% (n=33)	ref	--
Intervention Arm 1: Home BP monitor	55.6% (n=56)	37.0% (n=29)	1.490 [0.463, 4.794]	0.504
Intervention Arm 2: Nurse-administered behavior intervention	56.8% (n=65)	43.8% (n=36)	2.220 [0.727, 6.780]	0.161
Intervention Arm 3: Combined intervention	59.5% (n=55)	52.4% (n=29)	3.546 [1.01, 12.476]	0.049

*change in number of participants due to loss of follow-up
°usual care is referent group

We also evaluated literacy's interaction with the intervention effect on 24-month reported adherence to determine whether medication nonadherence changed differently for participants of low vs. adequate literacy. There did not appear to be any significant

difference between groups' odds of nonadherence over 2 years when evaluating literacy's interaction with the intervention effect, though there was a trend toward statistical significance. All high literacy participant groups had a decrease in adherence over 2 years, and it did not appear that there was a significant difference in the odds of nonadherence for any group relative to usual care. This finding suggests that for patients with adequate literacy, the interventions tested do not target medication adherence more effectively than usual care. Similarly, self-reported medication adherence improved in all randomized groups for low-literacy participants. There was a significant odds of nonadherence over 2 years for low-literacy participants receiving the combined intervention relative to usual care. The usual care group of low-literacy participants reported the most improvement in adherence over 2 years, suggesting that the home BP monitoring and nurse-administered behavioral interventions, and those two combined, are not as effective at increasing medication adherence for low-literacy patients. These findings support the suggestions from previous research that despite interventions being effective, they do not seem to lead to large improvements in adherence.[6]

The findings of this study are consistent with previous randomized controlled trials and systematic reviews on medication adherence. No interventions have shown consistent improvements in medication adherence across studies. Combined educational and behavioral interventions are often utilized and suggested. The nurse-administered intervention combined both educational and behavioral strategies, targeting self-management of chronic disease through a tailored intervention. The home BP monitoring intervention was a behavioral intervention. Research remains inconclusive as to whether behavioral, educational, or combined interventions are most effective for improving medication adherence.[1, 4] Each participant group reported improvement in

antihypertensive medication adherence. This finding could imply that all interventions worked equally well or that the interventions are not more effective than usual care at improving medication adherence. In a review of medication adherence interventions on participants with multiple chronic conditions, individuals in the control and intervention group became more adherence suggesting that the Hawthorne effect rather than any particular intervention leads to improved medication adherence.[5]

We also evaluated the intervention effect for adequate and low-literacy patients. The improvement in adherence across trial arms but lack of significant odds of nonadherence between groups is consistent with current literature. Interventions targeting low-literacy populations have mixed results. Some interventions are more effective for either high- or low-literacy groups, while others improve outcomes for patients regardless of literacy level.[11] In this trial the odds of nonadherence were significantly greater for low-literacy participants in the combined intervention arm. In a recent review of complex interventions for low-literacy populations, combined interventions were overall more effective for the intervention group.[11] Our findings do not seem to support this conclusion, however the large improvement in self-reported adherence in low-literacy participants of the usual care group is not completely understood and this may have contributed to the significant nonadherence odds ratio in this particular subgroup.

There are a few limitations of this study that should be considered when interpreting the results of this study. First, the interventions were not designed to improve medication adherence but to improve blood pressure control. While improvements in adherence can lead to improved blood pressure outcomes, interventions that improve medication adherence have shown variable effects on blood pressure outcomes.[6] Second, the loss of follow-up for 150 participants means that final self-reported medication

adherence could not be collected. More of these loss-to-follow-up participants had low health literacy (n=100), which could have an effect on the stratified nonadherence odds ratio outcome. Third, low-literacy participants differed from adequately-literate participants on a number of reported characteristics. This was accounted for in part by randomization being stratified by literacy level. In stratifying the groups by literacy, we did not evaluate the effect of these characteristics on effect of the intervention on 24-month medication adherence. Lastly, self-reported medication adherence was the measure used to assess participants adherence to their antihypertensive medications. While this measure is commonly used, it may not be accurate or precise in assessing true adherence compared to pill counts, electronic pill caps, checking pharmacy refill records, or other less subjective measures. We recognize that a more objective tool for evaluation medication adherence may affect the outcome measure.

In conclusion, there was little evidence that home BP monitoring, a nurse-tailored behavioral intervention, or the combination of these two interventions has a significant effect on medication adherence relative to usual care. Despite the findings in a recent review that complex interventions are more effective for improving health outcomes in low-literacy patients, we found significantly higher odds of nonadherence for low-literacy patients in the combined intervention group. Further studies are needed to determine the best strategies to target medication adherence and to improve medication adherence in low-literacy patients. Given that low health literacy and low medication adherence rates place individuals at increased risk for poor health outcomes, finding effective interventions is important.

Addenda

Literature Review Results

Citation	Study Design	Health Literacy Measure	Intervention	Setting/Population	Follow-up duration	Outcome Description	Results	Quality Rating
Clement S, Ibrahim S, Crichton N, Wolf M, Rowlands G. Complex interventions to improve the health of people with limited literacy: A systematic review. Patient Education and Counseling June 2009;75(3):340-51.**	systematic review	REALM, S-TOFHLA, ABLE, WRAT, Ten Have word recognition measure, education level, ESL class attendance, asking about ability to read, a few studies did not assess literacy	2 interventions for health professionals, 1 focused on literacy education, 12 health education/management; most common elements of interventions (in 3 or more studies): verbal presentation, material in simplified language, pictorial information, checking for participant understanding, spacing information, audiotapes, videotapes, and care management	Adults of mixed literacy levels (health professionals, participant	follow-up ranged from immediately following the intervention to 10.5 months	aim of this review was to evaluate the effects of multi-faceted interventions intended to improve health-related outcomes in individuals with limited literacy	knowledge and self-efficacy were most likely to improve with these complex interventions, 13/15 trials had at least 1 significant different in primary outcomes favoring the intervention group, some decrease in physician satisfaction and potential increased cost of these interventions, qualityof the studies was variable	good/fair
Conn VS, Hafdahl AR, Cooper PS, Ruppar RM, Mehr DR, Russel CL. Interventions to Improve Medication Adherence Among Older Adults: Meta-Analysis of Adherence Outcomes Among Randomized Controlled Trails. The Gerontologist 2009 May	meta-analysis	not specified, though literacy was one of the patient characteristics considered	interventions in at least 2 of the 33 studies included (frequency): drug education(23), written instructions(10), dose modification(7), disease education(6), medication review(6), packaging(4), succinct written instructions(4), tailored intervention(4), medication self-monitoring(2), written calendar(2), disease symptom self-monitoring(2), intergration of provider care(2)	11,827 participants from RCTs between 1970 and 2007 whose median age was 67	follow-up varied by study from a single intervention session (15minutes) to several weeks	primary outcome was medication adherence effect size, secondary outcomes included medication adherence interventions' effects on medication and disease knowledge, health	medication adherence ES = 0.33 ($p<0.001$); positive moderators from interventions of medication adherence included special packaging of medications, dose modification, and stimulus prompting; significant ES were also seen for knowledge (ES=0.48, $p<0.001$) and diastolic BP (ES=0.19, $p<0.05$); medication adherence was unrelated to participants' age, income, cognitive status, literacy or chronic illnesses	good

21;49(4):447-62.						outcomes, and health service utilization		
Cordasco KM, Asch SM, Bell DS, Guterman JJ, Gross-Shulman S, Ramer L, Elkayam U, Franco I, Leatherwood CL, Mangione CM. A low-literacy medication education tool for safety-net hospital patients. Am J Prev Med. 2009 Dec;37(6 Suppl 1):S209-16.	randomized controlled trial	TOFHLA	low-literacy icon- and picture-based medication tool to help with medication regimine schedules given by nurse upon hospital discharge	Southern California safety-net hospital, patients discharged after evaluation of or treatment for CHF or CAD	2-week and 4-week interviews	primary outcome was self-reported medication adherence 2 weeks after hospital discharge	control group: 0.5 doses missed, no correlation between self-reported adherence and pill count, 78% adherent intervention group: 1.1 doses missed, correlation between self-reported adherence and pill count, 70% adherent	poor
Mullan RJ, Montori VM, Shah ND, et al. The diabetes mellitus medication choice decision aid: a randomized trial. Archives of internal medicine 2009;169(17):1560-68.	randomized controlled trial	education level	decision aid with 6 cards describing 6 effects (weight change, hypoglycemia, change in HgbA1C, daily routine, monitoring, side effects) of 5 diabetes medications used by clinicians in outpatient visit with diabetic patients	adult diabetes patients with diagnosis at least 1 year taking at most 3 diabetes medications and with HgbA1C between 7 and 9.5% being seen by clinicians (faculty physicians, resident, physician assistants, nurse practicioners) in	1 visit-intervention with 1mo, 3mo, and 6month follow-up	primary outcomes were: patients feeling involved in the decision-making process, medication adherence at 6 months, and change in HgbA1C at 6 months post-	patients in the intervention group did not score higher on the Decisional Conflict Scale, but they did have more knowledge about medications; medication adherence was close to perfect in both groups by self-report and pharmacy records but the control group had a higher adherence rate (81%) vs the decision-aid group (76%) [OR .74, 95%CI 0.24 to 2.32]; there was no effect	good

				either outpatient or family medicine clinics in the Mayo Clinic or Olmstead Medical Center health systems		intervention	on HgbA1C for either gorup	
Murray MD, Young J, Hoke S, Tu W, Weiner M, Morrow D, Stroupe KT, Wu J, Clark D, Smith F, Gradus-Pizlo I, Weinberger M, Brater DC. Pharmacist intervention to improve medication aherence in heart failure: a randomized trial. Ann Intern Med. 2007 May 15;146(10):714-25.	randomized controlled trial	none	pharmacist gave written and verbal instructions and was available to answer questions regularly from participants, icons on written instructions and container label and lid, low-literacy timeline for drug regimine	Wishard Health Services primary care and cardiology services and hospital, patients of low-income with state/local assistance to pay for their medications	9-month intervention and 3-month post-intervention observation; 3, 6, and 12 month interviews and monthly telephone survery	primary outcome was adherence measured with electronic prescription monitors (MEMS lids) and HF exacerbations requiring ED visits or hospitalization	taken adherence significantly different with 78.8% vs 67.9% for intervention vs usual care group, respectively (95% CI: 5.0, 16.7); scheduling adherence significantly different at 53.1% vs. 47.2% for intervention vs usual care (95% CI 0.4, 11.5); refill adherence significantly different at 109.4% vs 105.2% for intervention vs usual care (p=.007) 3-mo post intervention: taking adherence and scheduling adherence no longer significantly different between intervention and usual care groups	good

Peterson AM, Takiya L, Finley R. Meta-analysis of trials of intervention to improve medication adherence. Am J Health - Syst Pharm 2003 Apr 1;657-65.*	meta-analysis (from citation in Conn article)	not discussed	behavioral interventions included dosage schedule change, packaging chance, skill buidling by health care professional, mail or email or telephone reminders, calendars, pill counting and pillboxes, and rewards; educational interventions included oral education by a physician or nurse or pharmacist, audiovisual education, written instructions, telephone education, and mailed or emailed instructions	patients taking some medication for various diseases, mostly adults aged 19 to 65, males and females, 26% of studies focused on patients with hypertension	mean follow-up was 4.5 months, ranged from 14 days to 1 year	aim of this review was to identify and study the effects of tools and methods designed to improve medication adherence in randomized controlled trials	overall adherence improved 4-11%, there was no significant different among behavioral or educational interventions, among the combined intervention trials mail reminders had the largest impact (ES = 0.38)	good
Pignone M, DeWalt DA, Sheridan S, Berkman N, Lohr KN. Interventions to Improve Health Outcomes for Patients with Low Literacy: A Systematic Review. J Gen Intern Med 2005;20:185-192.	systematic review	studies included used REALM, WRAT, Adult Basic Learning Examination, Gates-MacGinitie, ABLE, Comprehensive Adult Student Assessment Scale	information pamphlets, brochures and forms written for lesser grade level or using photographs; computer-generated discharge instructions; CD-ROM; instructional and interactive videos; package label; verbal teaching; educational classes/programs	included studies were in developing countries, sample sizes ranged from 28-1,744 participants	study and trial lengths vavied; all studies reviewed between 1980-2003	aim of this review was to identify and evaluate interventions designed to improve health outcomes that are associated with low literacy	quality ratings: 10 good, 9 fair, and 1 poor studies mixed results with slight improvement or no effect on health knowledge, biochem/biomarkers, health behavior, preventive services use, and disease incidence/prevalence/severity; some interventions worked best for low-literacy participants, some for high, and some for both	good

Rudd RE, Blanch DC, Gall V, et al. A randomized controlled trial of an intervention to reduce low literacy barriers in inflammatory arthritis management. Patient education and counseling 2009;75(3):334-39.	randomized controlled trial	A-REALM, education level (more vs less than high school education)	individualized intervention including usual care, plain english notebook with information about arthritis and medications and management (5th - 8th grade reading level), and 2 appointments + desired follow-up with arthritis educator; for first year there was a plain english randomized group that consisted of usual care + plain english notebook (13 patients, added to individualized intervention group)	127 adult patients with rheumatoid arthritis, psoriatic arthritis, or inflammatory polyarthritis receiving care at large urban teaching hospital clinics by rheumatologist	time of intervention unclear but follow-up 6months and 12months post-intervention	primary outcomes: medication adherence, self-efficacy, patient satisfaction, and appointment keeping secondary outcomes: health status, mental health	there was no significant difference between the intervention and standard care groups for any of the primary outcomes at 12 months; mental health improved at 6 months for the intervention group (4.56% increase vs. 4.32% decrease for intervention vs control group on mental health index); of note medication adherence decreased in both groups by 12 months though the difference between the groups was not significant	fair
Schroeder K, Fahey T, Ebrahim S. How Can We Improve Adherence to Blood Pressure-Lowering Medication in Ambulatory Care? - Systematic Review of Randomized Controlled Trials. Arch Intern Med 2004 Apr 12;164:722-732.*	systematic review	not discussed	simplifying dosing regimens, patient education, patient moviation/support/reminders, and complex or combined interventions	15,519 adults with essential hypertension	ranged from 2 to 60 months	aim of this review was to determine which types of interventions are most effective to increasing adherent to BP medications	simplifying dosing regimens was the best overall strategy increasing adherence 7 to 19.6% in 7 out of 9 studies; motivational/support and complex interventions led to small increases in adherence; education only interventions were not very successful; poor methodology was noted in most studies and makes definitive conclusions about the best strategies difficult	good

Williams A, Manias E, Walker R. Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review. Journal of Advance Nursing 2008;63(2):132-43.	systematic review	not discussed	interventions utilized educational and behavioral approaches, 7/8 included studies had a pharmacist-delivered intervention combining adeucation, personal or telephone follow-up, referral or adjusted medication regimens, and reminders to participants to take their medications; 1 intervention used a medication discharge plan and counseling	adults with at least 3 chronic conditions	follow-up was at least 3 months for inclusion in this review	aim of this review was to identify research involving medication adherence interventions for people with multiple chronic conditions	periodic reinforcement is needed to maintain medication adherence behavior change, psychosocial interventions are needed, it is important to assess participants' perspective of adherence outcomes, more valid measures of medication adherence need to be consistently utilied and potentially developed	good

ABLE – Adult Basic Learning Examination
REALM – Rapid Estimate of Adult Literacy (A-REALM is arthritis modification)
TOFHLA – Test of Functional Health Literacy in Adults (S-TOFHLA is shortened version)
WRAT – Wide Range Achievement Test
* = found in citation of an included study
** = faculty recommendation

Literature Search Table

Date	Database	Main search terms	Modifiers	Yield (articles)	Used search?
3/12/2010	Google scholar	medication adherence interventions	n/a	81300	No
3/12/2010	Google scholar	medication adherence low literacy	n/a	7820	No
3/21/2010	Google scholar	low literacy hypertension medication adherence intervention	n/a	2870	No
3/28/2010	Google scholar	low literacy hypertension medication adherence intervention	2005-2010	1150	No
6/12/2010	Pubmed	health literacy hypertension	clinical trials	51	yes until re-defined question
6/12/2010	Google scholar	health literacy hypertension medication adherence clinical trials	medicine/pharm/vet science; 2001-2010, english language	704	yes until re-defined question
6/17/2010	Google scholar	low literacy interventions clinical trials	since 2004; articles only, english language, medicine/pharm/vet science	1270	yes until re-defined question
6/18/2010	Pubmed	educational status hypertension	clinical trials, english languge, adults 19+ years old, since 2004	16	No
6/18/2010	Pubmed	MeSH: health literacy medication adherence		22	No
6/18/2010	Google scholar	low literacy clinical trials medication adherence hypertension	articles since 2000, medicine/pharm/vet science, english language	733	No
6/28/2010	Pubmed	MeSH: educational status medication adherence		22	No
6/28/2010	Google scholar	medication adherence literacy interventions	medicine/pharm/vet science, articles only, since 2000	2000	No

		medication adherence literacy interventions clinical trials	medicine/pharm/vet science, articles only, since 2000	1630	Yes
6/30/2010	Pubmed	medication adherence literacy	clinical trials, english language, adults 19+	30	Yes

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